INDUSTRIAL PROPERTY REGISTRY SPAIN	PRIORITY DATA A1 31 NUMBER 32 DATE 33 COUNTRY	12 PATENT
		21 APPLICATION NUMBER 547442
		22 DATE OF SUBMISSION 30 SEPT 1985

71 APPLICANT(S) NATIONALITY

Consejo Superior Investigaciones Científicas Spanish

REGISTERED OFFICE

Serrano, 117 Madrid

72 INVENTOR(S)

Carlos Corral Saleta and Jaime Lissavetzky Díez

73 PROPRIETOR(S)

Consejo Superior Investigaciones Científicas

11 PUBLICATION No. 8701172	45 PUBLICATION DATE	62 PATENT OF WHICH IT IS DIVISIONAL	GRAPHIC (ONLY FOR INTERPRETING ABSTRACT)

51 Int. Cl

Int. Cl.[4] C07D409/04//A61K31/38,31/41,31/415

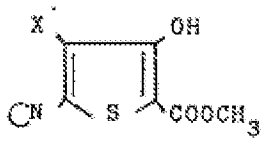
54 TITLE

"Process for the preparation of 3-hydroxy-5-(1-polyazolyl)-2-methoxycarbonylthiophene derivatives"

57 ABSTRACT (VOLUNTARY CONTRIBUTION, WITH NO LEGAL VALUE)

DESCRIPTION

The present invention relates to a process for the preparation of a series of compounds characterised by the general formula I, which may be useful as intermediate or end products in the synthesis of new therapeutic agents

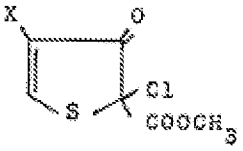


I

I

in which X represents a hydrogen atom or a halogen atom and ⊂N[1] any polyazole or benzopolyazole heterocycle.

The process to which this invention relates is characterised in that compounds whose structure corresponds to the general formula (II) below



II

II

in which X represents a hydrogen atom or a halogen atom, and which is obtained from 3-hydroxy-2-methoxycarbonylthiophene or any of its 4-halogenated derivatives of an embodiment already described, are made to react at ambient temperature with a double quantity of a polyazole or benzopolyazole heterocycle in the presence of solvent, to produce the compounds with general formula I.

[1] Translator's note: I do not know what these hand-written symbols ⊂ and ⊃ in the text represent but have reproduced them to the best of my ability.

In all cases the reaction takes place by 1,4 addition of the NH group of the heterocycle to the α, β-enonic system of compounds II and subsequent spontaneous loss of hydrogen chloride by γ elimination, which is collected by the excess of heterocycle present in the reaction, to produce compounds I.

It will be easily understood that these stages which constitute the essential part of the invention can be brought to a conclusion, using solvents, reagents, catalysts and very varied experimental conditions, but which are obvious for any specialist and consequently any logical change of these factors has to be considered included in the essential part of the invention.

Therefore the conditions which are given in the illustrative examples, although preferred for practical reasons, must not be considered as the only ones used or claimed in the present invention.

EXAMPLE 1

Preparation of 3-hydroxy-5-(1-pyrazolyl)-2-methoxycarbonyl-thiophene. (I, X=H, ⊂N=1=pyrazolyl)

1.2 g (0.018 moles) of pyrazole were added to a dissolution of 1.7 g (0.009 moles) of 2-chloro-2-methoxycarbonyl-3-oxo-2,3-dihydrothiophene (II, X=H) in 10 ml of acetic acid. The reaction mixture was left for 2 days at ambient temperature and the crystallised solid was filtered and washed with acetic acid, and a colourless solid was obtained with a melting point 161-163ºC. The concentration of the mother liquors made it possible to obtain more quantity of this solid.

A sample was recrystallised from acetic acid increasing the melting point to 162-164ºC.

Analysis (%)

Calculated for $C_9H_8N_2O_3S$	C 48.21;	H 3.57;	N 12.50
Found	48.37	3.71	12.63

EXAMPLE 2

Preparation of 3-hydroxy-5-(1-imidazolyl)-2-methoxycarbonyl-thiophene. (I, X=H, ⊂N=1-imidazolyl)

0.35 g (0.0052 moles) of imidazole dissolved in 3 ml of chloroform were added to a dissolution of 0.5 g (0.0026 moles) of 2-chloro-2-methoxycarbonyl-3-oxo-2,3-dihydrothiophene (II, X=H) in 3 ml of chloroform. The reaction mixture was left at ambient temperature and evaporated to dryness. The residue was treated with water

and benzene and from the evaporation of the benzene phase a solid was obtained which was recrystallised from ethyl acetate or acetic acid. Melting point 112-113°C.

Analysis (%)

Calculated for $C_9H_8N_2O_3S$	C 48.21;	H 3.57;	N 12.50
Found	48.49	3.71	12.39

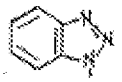
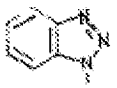
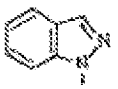
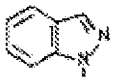
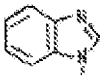
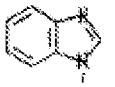
EXAMPLES 3 TO 10

Starting from 2-chloro-2-methoxycarbonyl-3-oxo-2,3-dihydrothiophene (II, X=H) or its chlorinated derivative (II, X=Cl) and using the same experimental conditions as in example 1, the products indicated in the Table were obtained.

EXAMPLES 11 TO 13

Starting from 2-chloro-2-methoxycarbonyl-3-oxo-2,3-dihydrothiophene (II, X=H) or its chlorinated derivative (II, X=Cl) and using the same experimental conditions as in example 2 the products indicated in the Table were obtained.

TABLE

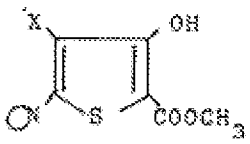
Example No.	N	X	Melting point (°C)	Analysis	%C	%H	%N
3		Cl	136-138[a]	Calculated	41.77	2.71	10.83
				Found	41.83	3.00	11.07
4		H	166-167[b]	Calculated	42.66	3.11	18.66
				Found	42.51	3.07	18.48
5		Cl	171-173[a]	Calculated	36.99	2.31	16.18
				Found	37.13	2.56	16.33
6		H	185-187[b]	Calculated	52.36	3.27	15.27
				Found	52.08	3.21	15.43
7		Cl	144-146[b]	Calculated	46.53	2.58	13.57
				Found	46.71	2.73	13.46
8		H	183-185[b]	Calculated	56.93	3.65	10.22
				Found	57.09	3.56	10.43
9		Cl	194-196[b]	Calculated	50.57	2.92	9.08
				Found	50.65	2.86	9.41
10		H	211-213[b]	Calculated	47.24	3.94	11.02
				Found	47.07	4.12	11.31
11		Cl	173-175[a]	Calculated	41.78	2.71	10.83
				Found	41.93	2.87	11.02
12		H	90-92[b]	Calculated	56.93	3.65	10.22
				Found	57.12	3.49	10.31
13		Cl	144-146[b]	Calculated	50.57	2.92	9.08
				Found	50.71	3.05	9.17

[a]Recrystallised from methanol. [b]Recrystallised from acetic acid.

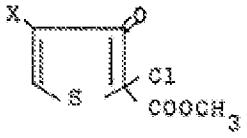
CLAIMS

Claimed as of novel and own invention is the property and exclusive exploitation of:

1) "PROCESS FOR THE PREPARATION OF 3-HYDROXY-5-(1-POLYAZOLYL)-2-METHOXYCARBONYLTHIOPHENE DERIVATIVES" with general formula



in which X represents a hydrogen atom or a halogen atom and ⊂N any polyazole or benzopolyazole heterocycle, characterised in that the compounds which have the following general formula



in which X represents a hydrogen atom or a halogen atom are made to react at ambient temperature with a double quantity of a polyazole or benzopolyazole heterocycle with formula H-N⊃, in the presence of solvent, to give rise to compounds with general formula I.

2) A process according to claim 1, characterised in that it uses 2-chloro-2-methoxycarbonyl-3-oxo-2,3-dihydrothiophene as starting material.

3) A process according to claim 1, characterised in that it uses 2,4-dichloro-2-methoxycarbonyl-3-oxo-2,3-dihydrothiophene as starting material.

4) A process according to claim 1, characterised in that it uses pyrazole as reacting heterocycle.

5) A process according to claim 1, characterised it that it uses 1,2,4-triazole as reacting heterocycle.

6) A process according to claim 1, characterised it that it uses imidazole as reacting heterocycle.

7) A process according to claim 1, characterised it that it uses benzotriazole as reacting heterocycle.

8) A process according to claim 1, characterised it that it uses indazole as reacting heterocycle.

9) A process according to claim 1, characterised it that it uses benzimidazole as reacting heterocycle.

10) "PROCESS FOR THE PREPARATION OF 3-HYDROXY-5-(1-POLYAZOLYL)-2-METHOXYCARBONYLTHIOPHENE DERIVATIVES" as described in the main part of this description and claims which consist of 7 pages written on just one side.

Madrid, 30 SEPT. 1985

(Signature)